IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

Inventor(s): FAULL, Alan W. et al

Filed: Herewith

Title: ANTI-INFLAMMATORY INDOLE DERIVATIVES

July 18, 2001

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE SPECIFICATION:

At the top of the first page, just under the title, insert

☒ --This application is the National Phase of International Application PCT/GB00/00260 filed January 31, 2000 which designated the U.S. and that International Application

☒ was ☐ was not published under PCT Article 21(2) in English.--

Respectfully submitted,

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ANTI-INFLAMMATORY INDOLE DERIVATIVES

The present invention relates to chemical compounds, to their production as well as to pharmaceutical compositions containing them as well as to their use in therapy, in particular of inflammatory disease.

MCP-1 is a member of the chemokine family of pro-inflammatory cytokines which mediate leukocyte chemotaxis and activation. MCP-1 is a C-C chemokine which is one of the most potent and selective T-cell and monocyte chemoattractant and activating agents known. MCP-1 has been implicated in the pathophysiology of a large number of inflammatory diseases including rheumatoid arthritis, glomerular nephritides, lung fibrosis, restenosis (International Patent Application WO 94/09128), alveolitis (Jones et al., 1992, *J. Immunol.*, **149**, 2147) and asthma. Other disease areas where MCP-1 is thought to play a part in their pathology are atherosclerosis (e.g. Koch et al., 1992, *J. Clin. Invest.*, **90**, 772 -779), psoriasis (Deleuran et al., 1996, *J. Dermatological Science*, **13**,. 228-236), delayed-type hypersensitivity reactions of the skin, inflammatory bowel disease (Grimm et al., 1996, *J. Leukocyte Biol.*, **59**,. 804-812), multiple sclerosis and brain trauma (Berman et al, 1996, *J. Immunol.*, **156**,. 3017-3023). An MCP-1 inhibitor may also be useful to treat stroke, reperfusion injury, ischemia, myocardial infarction and transplant rejection.

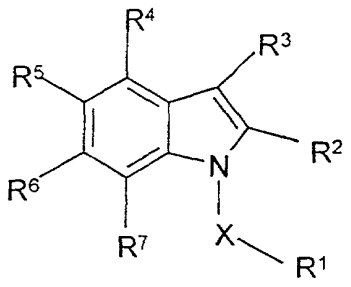
MCP-1 acts through the MCP-1 receptor (also known as the CCR2 receptor). MCP-2 and MCP-3 may also act, at least in part, through the MCP-1 receptor. Therefore in this specification, when reference is made to "inhibition or antagonism of MCP-1" or "MCP-1 mediated effects" this includes inhibition or antagonism of MCP-2 and/or MCP-3 mediated effects when MCP-2 and/or MCP-3 are acting through the MCP-1 receptor.

Copending International Patent Application Nos. PCT/GB98/02340 and PCT/GB98/02341 describe and claim groups of compounds based upon the indole ring structure which are inhibitors of MCP-1 and therefore have applications in therapy.

The use of certain indole derivatives as NMDA antagonists is described is USP5051442, WO9312780, EP-483881. Other indoles and their use as inhibitors of leukotriene biosynthesis is described in for example, EP-A- 275-667.

The applicants have found a particular substitution on the indole ring produces advantageous results when used therapeutically as inhibitors of MCP-1.

According to the present invention there is provided a compound of formula (I)

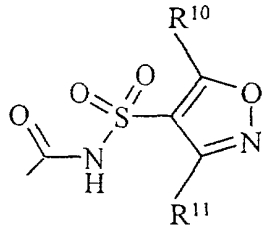


(I)

X is CH_2 or SO_2

R^1 is an optionally substituted aryl or heteroaryl ring;

R^2 is carboxy, cyano, $-C(O)CH_2OH$, $-CONHR^8$, $-SO_2NHR^9$, tetrazol-5-yl, SO_3H, or a group of formula (VI)



(VI)

where R^8 is selected from hydrogen, alkyl, aryl, cyano, hydroxy, $-SO_2R^{12}$ where R^{12} is alkyl, aryl, heteroaryl, or haloalkyl, or R^8 is a group-$(CHR^{13})_r$-COOH where r is an integer of 1-3 and each R^{13} group is independently selected from hydrogen or alkyl; R^9 is hydrogen, alkyl, optionally substituted aryl such as optionally substituted phenyl or optionally subtituted heteroaryl such as 5 or 6 membered heteroaryl groups, or a group COR^{14} where R^{14} is alkyl, aryl, heteroaryl or haloalkyl; R^{10} and R^{11} are independently selected from hydrogen or alkyl, particularly C_{1-4} alkyl;